SCHEDULING STATUS:

S4

PROPRIETARY NAMES (AND DOSAGE FORMS):

ABITREXATE 50 Injection

ABITREXATE 500 Injection

ABITREXATE 1 g Injection

ABITREXATE 5 g Injection

COMPOSITION:

Abitrexate 50 and Abitrexate 500: Each 1 ml contains methotrexate 25 mg

Abitrexate 1 g: Each 10 ml contains methotrexate 1 g

Abitrexate 5 g: Each 50 ml contains methotrexate 5 g

PHARMACOLOGICAL CLASSIFICATION:

A26 Cytostatic agents

PHARMACOLOGICAL ACTION:

Methotrexate is an antineoplastic agent, which acts as an antimetabolite of folic acid. It also has immunosuppressant qualities.

When given in low doses, methotrexate is well absorbed from the gastro-intestinal tract. Higher doses are less well absorbed. It is distributed mainly in the extracellular spaces but a proportion penetrates cell membranes and is strongly bound to dihydrofolate reductase. Only small amounts of methotrexate diffuse into the cerebrospinal fluid but higher concentrations are achieved with high doses. About 50 % is bound to plasma proteins. Biphasic and triphasic clearance from plasma has been reported. The majority of a dose is excreted unchanged in the urine within 24 hours and up to 15 % may appear in the bile although because of re-absorption less may be excreted in the

faeces. Bound methotrexate may be retained in the body for many months.

INDICATIONS:

- Lymphoblastic leukaemia in children and meningeal leukemia.
- Choriocarcinoma and related trophoblastic tumours of women.
- Women with non-metastatic trophoblastic disease, hydatidiform mole and chorioadenoma destruens.
- Carcinomas of the breast, tongue, pharynx and testes (in conjunction with chlorambucil and dactinomycin).
- Carcinoma of the lung and osteogenic sarcomas (high dose **ABITREXATE** with folinic acid rescue).
- Treatment of severe psoriasis (see Warnings).
- Prevention of graft-versus-host reactions that result from marrow transplantation.
- Dermatomyositis, rheumatoid arthritis (not adequately responding to other therapy), Wegener's granulomatosis and pityriasis rubra pilaris.

CONTRA-INDICATIONS:

- Hypersensitivity to methotrexate.
- **ABITREXATE** is contra-indicated in pregnancy and in lactation. (See pregnancy and lactation).
- **ABITREXATE** is contra-indicated in patients with psoriasis or rheumatoid arthritis with serious renal or liver disorders, bone marrow hypoplasia, leucopenia, thrombocytopenia, anaemia, and alcohol abuse.
- Safety and efficacy in children have not been established other than in cancer chemotherapy.

WARNINGS:

ABITREXATE should be administered under the supervision of a medical doctor experienced in the use of chemotherapeutic agents.

ABITREXATE is an irritant; avoid contact with skin and mucous membranes.

Deaths have been reported with the use of **ABITREXATE** in the treatment of psoriasis and rheumatoid arthritis. In the treatment of psoriasis and rheumatoid arthritis, **ABITREXATE** should be restricted to severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or dermatological consultation.

INTERACTIONS:

The effects of **ABITREXATE** may be enhanced by concurrent administration of aminobenzoic acid, chloramphenicol, phenylbutazone, phenytoin, probenecid, salicylates, sulphonamides, doxorubicin, bleomycin, cyclophoshamide, aminoglycosides, allopurinol, vincristine, hydrocortisone, prednisone, asparaginase, cytosine arabinoside and tetracyclines.

Non-steroidal anti-inflammatory drugs (NSAIDS) should not be administered prior to or simultaneously with high dose **ABITREXATE** treatment (>10 mg methotrexate per week).

Increased serum levels of **ABITREXATE** have been reported at simultaneous administration of some NSAIDS with high dose **ABITREXATE** resulting in death by serious haematologic or gastro-intestinal toxicity.

NSAIDS, salicylates and other weak organic acids, like probenecid, can lower tubular secretion of **ABITREXATE** resulting in increased toxicity. Use of **ABITREXATE** with these drugs should be made carefully under strict supervision. The potential toxicity of **ABITREXATE** is increased in particular with simultaneous use of NSAIDS when diuretics are also used. In rheumatology, a combination therapy of low-dose **ABITREXATE** and a NSAID is commonly used.

Care should be taken in combining high dose **ABITREXATE** with potentially nephrotoxic therapy (e.g. cisplatin).

Oral antibiotics (including tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics) may influence the intestinal flora and inhibit **ABITREXATE** (re) absorption.

Interaction with therapeutic radiation may occur. In combination with other cytostatic medicines pharmacodynamic interactions may occur; resulting in increased therapeutic activity and increased toxicity.

No vaccination with live virus vaccines should be performed in patients receiving **ABITREXATE.** Partial or total protection can be obtained through inactivated vaccines.

In some cases a potentiation of bone marrow suppression in patients treated with **ABITREXATE** by trimethoprim/sulphamethoxazole has been reported, probably by additional folic acid antagonism. The combined use of **ABITREXATE** and sulphonamides is therefore strongly advised against.

Vitamin preparations containing folic acid or folic acid derivatives may decrease the effect of systemically administered **ABITREXATE.** Preliminary human and animal studies have shown that after intravenous administration of calcium folinate a small amount penetrates into the cerebrospinal fluid, predominantly as 5-methyltetrahydrofolate, and this amount is a factor 1 to 3 lower than the normal **ABITREXATE** concentration after intrathecal administration. Nevertheless high doses of calcium folinate may lower the effectivity of intrathecally administered **ABITREXATE.** Folate deficiencies may increase **ABITREXATE** toxicity.

PREGNANCY AND LACTATION:

ABITREXATE must not be used during pregnancy and lactation. See Contra-indications and Side-effects (Urogenital and Other disorders)

DOSAGE AND DIRECTIONS FOR USE:

ABITREXATE may be given by mouth, or by injection. The dose of **ABITREXATE**, the dosage frequency, the total dose and combination with other cytostatic medicine and/or folinic acid are subject to frequent modification as scientific knowledge improves.

Lymphoblastic leukaemia: When used for induction, **ABITREXATE** in doses of 3,3 mg/m^2 in combination with prednisone 60 mg/m^2 given daily produced remission in 50 % of patients treated, usually within a period of 4 to 6 weeks. **ABITREXATE** alone or in combination with other agents appears to be the medicine of choice for securing maintenance of medicine-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: **ABITREXATE** is administered twice weekly either by mouth or intramuscularly in doses of 30 mg/m^2. It has also been given in doses of 2,5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regime.

Meningeal leukaemia: Some patients with leukaemia are subject to leukaemic invasion of the central nervous system. This may manifest characteristic signs or symptoms or may remain silent and be diagnosed only by examination of the cerebrospinal fluid which contains leukaemic cells in such cases. Therefore, the CSF should be examined in all leukaemic patients. Since passage of **ABITREXATE** from blood serum to the cerebrospinal fluid is minimal, for adequate therapy the medicine is administered intrathecally. A common approach is to treat such patients as may actually manifest leukaemic involvement by direct intrathecal instillation of **ABITREXATE**.

Intrathecal administration: NOTE: For convenience, and to minimise the risk of overdosage, it is recommended that vials containing 50 mg of preservative-free **ABITREXATE**, be used for intrathecal administration. Administration is at intervals of 2 to 5 days and is usually repeated until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advised. Large doses may cause convulsions.

The following dosage regimen is based on age instead of body surface area:

Age (years)	Dose (mg)
< 1	6
1	8
2	10
3 or older	12

Similar doses are given prophylactically to patients with lymphoblastic leukaemia, often in association with cranial irradiation. **ABITREXATE** in intravenous doses of about 500 mg per m^2, followed by folinic acid rescue, may also produce effective concentrations in the CSF.

Choriocarcinoma and similar trophoblastic diseases: Doses of 15 to 30 mg daily by mouth or intramuscularly for 5 days, at intervals of 1 to 2 weeks for 3 to 5 courses. Alternatively, 0,25 to 1 mg per kg body-weight up to a maximum of 60 mg has been given intramuscularly every 48 hours for 4 doses, followed by folinic acid rescue, and repeated at intervals of 7 days.

Since hydatidiform mole may precede or be followed by choriocarcinoma, prophylactic chemotherapy with **ABITREXATE** has been recommended. Chorioadenoma destruens is considered to be an invasive form of hydatiform mole. **ABITREXATE** administered in these disease states in doses similar to those recommended for choriocarcinoma.

Breast carcinoma: Prolonged cyclic combination chemotherapy with cyclophosphamide, **ABITREXATE** and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. **ABITREXATE** dosage was 40 mg/m^2 intravenously on the first and eighth days.

Combination chemotherapy may be necessary in patients with metastases.

A range of doses of **ABITREXATE** has been used in the management of solid tumours. Very high doses have been given by intravenous infusion, followed by folinic acid, in patients with osteogenic

sarcoma and carcinoma of the lung and of the head and neck.

Psoriasis: **ABITREXATE** has been given by mouth, intramuscularly, and intravenously in the treatment of psoriasis. Single weekly doses of 10 to 25 mg may be given by mouth or injection. Alternatively 2,5 mg has been administered by mouth every 12 hours for 3 doses or every 8 hours for 4 doses each week or 2,5 mg may be given daily by mouth for 5 days out of 7.

High-dose therapy: High dose therapy should be used only by qualified specialists in suitable hospital setting.

ABITREXATE RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF ABITREXATE

CLINICAL SITUATION	LABORATORY FINDINGS	FOLINIC ACID DOSAGE AND DURATION
Normal **ABITREXATE** elimination.	Serum **ABITREXATE** level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0,2 micromolar at 72 hours.	15 mg PO, IM or IV every 6 hours for 60 hours (10 doses starting at 24 hours after start of **ABITREXATE** infusion).
Delayed Late **ABITREXATE** elimination.	Serum **ABITREXATE** level remaining above 0,2 micromolar at 72 hours, and more than 0,05 micromolar at 96 hours after administration.	Continue 15 mg PO, IM or IV every 6 hours, until **ABITREXATE** level is less than 0,05 micromolar.
Delayed Early **ABITREXATE**	Serum **ABITREXATE** level of	150 mg IV every 3 hours, until

Elimination and/or Evidence of Acute Renal Injury.	50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100 % or greater increase in serum creatinine level at 24 hours after **ABITREXATE** administration (e.g., an increase from 0,5 mg/dL to a level of 1 mg/dL or more).	**ABITREXATE** level is less than 1 micromolar; then 15 mg IV every 3 hours, until **ABITREXATE** level is less than 0,05 micromolar.

GUIDELINES FOR ISOVORIN* METHOTREXATE RESCUE DOSAGE AND ADMINISTRATION.

CLINICAL SITUATION	LABORATORY FINDINGS	LEVOFOLINIC ACID DOSAGE AND DURATION
Normal **ABITREXATE** elimination.	Serum **ABITREXATE** level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0,2 micromolar at 72 hours.	7,5 mg PO, IM or IV every 6 hours for 60 hours (10 doses starting at 24 hours after start of **ABITREXATE** infusion).
Delayed Late **ABITREXATE** elimination.	Serum **ABITREXATE** level remaining above 0,2 micromolar at 72 hours, and more than 0,05 micromolar at 96 hours after administration.	Continue 7,5 mg PO, IM or IV every 6 hours, until **ABITREXATE** level is less than 0,05 micromolar.
Delayed Early **ABITREXATE**	Serum **ABITREXATE** level of	75 mg IV every 3 hours, until

Elimination and/or Evidence of Acute Renal Injury.	50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100 % or greater increase in serum creatinine level at 24 hours after **ABITREXATE** administration (e.g., an increase from 0,5 mg/dL to a level of 1 mg/dL or more).	**ABITREXATE** level is less than 1 micromolar; then 7,5 mg IV every 3 hours, until **ABITREXATE** level is less than 0,05 micromolar.

Mycosis fungoides: Therapy with **ABITREXATE** appears to produce clinical remissions in half of the cases treated. Dosage is usually 2,5 to 10 mg daily by mouth for weeks or months. Dose levels of medicine and adjustment of dose regime by reduction or cessation of medicine are guided by patient response and haematologic monitoring. **ABITREXATE** has also been given intramuscularly in doses of 50 mg once weekly or 25 mg twice weekly.

Rheumatoid arthritis: In case of intravenous or intramuscular administration of **ABITREXATE**, the starting dose in adults is 10 mg once weekly. If necessary, this dose can be increased in steps of 2,5 mg each until maximally a dose of 25 mg once weekly. Between the subsequent dose increases of each scheme there should be an interval of ca. 6 weeks. It is possible to administer parenterally a week before the initiation of therapy a test dose of 5 – 10 mg of **ABITREXATE** to detect idiosyncratic reactions of the patient.

In most patients improvement of the clinical situation occurs after 4 – 6 weeks. After about 6 months a plateau in the response is reached, whereafter sometimes modification of the dose is necessary to maintain this optimal clinical result.

After discontinuation of therapy a flare-up of rheumatoid arthritis may occur.

In case of oral administration of **ABITREXATE**, initially 2,5 mg to 5 mg every 12 hours for 3 doses once a week, the dosage being increased as necessary in increments of 2,5 mg per week up to a maximum of 20 mg per week or initially 10 mg once a week, the dosage being increased as necessary up to 20 mg per week.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

In general the incidence and severity of acute side effects is related to the dosage and frequency of administration. The *most frequent* adverse effects are ulcerative stomatitis, leucopenia, nausea and gastro-intestinal problems. Other *frequently* occurring side-effects are feeling unwell, inexplicable fatigue, chills and fever, dizziness and reduced resistance to diseases.

The undesirable effects with **ABITREXATE** are summarized by organ system.

Gastro-intestinal disorders:

Frequent: Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhoea, heamatemesis, melena, gastro-intestinal ulceration and bleeding and enteritis.

When vomiting, diarrhoea, or stomatitis occurs, with possible dehydration, **ABITREXATE** treatment should be discontinued until recovery. **ABITREXATE** should be used with extreme care in case of peptic ulcer or ulcerative colitis.

Haematological (Blood disorders):

Frequent: **ABITREXATE** may suppress haematopoiesis and cause anaemia, leucopenia and/or thrombocytopenia. In patients with existing haematopoietic insufficiencies **ABITREXATE** should be used with care, or not at all.

In psoriasis and rheumatoid arthritis treatment should be discontinued immediately in case of a significant drop in the blood count. In the treatment of neoplasia, **ABITREXATE** may only be continued if the possible cure justifies the risk of serious myelosuppression. Myelosuppression may also occur after intrathecal administration of **ABITREXATE**. Patients with serious granulocytopenia and fever should undergo immediate evaluation and usually require parenteral

broad-spectrum antibiotics.

Hepato-biliary disorders:

Less frequent: **ABITREXATE** may cause acute (increase in transaminases) or chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially lethal. It usually occurs after chronic use (mostly 2 years or longer) and after a total dose of at least 1,5 g.

In studies with psoriasis patients, hepatotoxicity appeared to be determined by the total cumulative dose. The effect is potentiated by alcoholism, obesity, diabetes and advanced age. A correct correlation has not yet been determined.

Information on progression and reversibility of lesions is not available. Care should be taken in the presence of existing liver damage or decreased liver function.

Liver function tests, including serum albumin should be carried out regularly prior to administration. Test results are often normal in cases of fibrosis and cirrhosis. These conditions can only be diagnosed by biopsy.

In case of psoriasis and rheumatoid arthritis it is recommended to perform a liver biopsy after a total cumulative dose of 1,5 g. Intermediate fibrosis or any cirrhosis usually prompts discontinuation of the therapy. Although mild changes usually are no reason to avoid or discontinue **ABITREXATE** treatment, the drug should be used with care.

Immune system disorders:

Less frequent: **ABITREXATE** should be used with extreme care in case of active infection and usually is contra-indicated in patients with immunodeficiency syndromes. During an **ABITREXATE** treatment immunisation may not be effective. Immunisation with live vaccine is usually not recommended. Disseminated vaccinia infections have been reported after a small pox immunization in patients undergoing **ABITREXATE** treatment. Hypogammaglobulinaemia has been observed less frequently.

Nervous system disorders:

Less frequent: Headache, drowsiness, blurred vision, aphasia, hemiparesis, paresis and convulsions have been reported after **ABITREXATE** administration.

There are reports of leucoencephalopathy after intravenous administration of **ABITREXATE** to patients who underwent craniospinal irradiation.

Chronic leucoencephalopathy was also reported in patients with osteosarcoma who were administered high dosages of **ABITREXATE** with calcium folinate rescue therapy, even without cranial irradiation. Discontinuation of **ABITREXATE** treatment does not always result in complete recovery.

A transient acute neurological syndrome has been observed in patients who underwent high dose **ABITREXATE** treatment. The clinical manifestations may consist of abnormal behaviour, focal sensomotoric phenomena, and abnormal reflexes. The exact cause of these symptoms is unknown.

After intrathecal administration of **ABITREXATE**, the possible toxic side-effects pertaining to the central nervous system may be classified in the following way:

- chemical arachnoiditis with symptoms such as headache, backache, neck stiffness and fever
- paresis, usually transient, with paraplegia involving one or more spinal nerve roots
- leucoencephalopathy with confusion, agitation, somnolence, ataxia, dementia and sometimes serious convulsions.

Respiratory (Pulmonary) disorders:

Less frequent: Death by interstitial pneumonitis has been reported and chronic interstitial obstructive lung disease sometimes occurred. Pulmonary symptoms (in particular a dry, non-productive cough) or a non-specific pneumonitis during the **ABITREXATE** treatment may indicate a potentially dangerous lesion and require discontinuation of the treatment and a thorough examination. Although symptoms may be varying, a patient with **ABITREXATE** induced lung disease typically shows fever, cough, dyspnoea, hypoxemia and infiltration in lung radiography. An

infection should be excluded. This condition may occur at any dosage. **ABITREXATE** related lung pathology has rarely been described after intrathecal administration of **ABITREXATE**. At the onset of **ABITREXATE** induced lung disease, the re-administration of **ABITREXATE** is contra-indicated.

Urogenital disorders:

Frequent: Serious nephropathy or renal insufficiency, azotemia, cystitis and haematuria, defective oognesis or spermatogenesis, transient oligospermia, menstrual dysfunction and vaginal discharge, infertility, abortion, foetal deviations, suppression of spermatogenesis, loss of libido, and impotence may occur.

High dosages of **ABITREXATE** may cause renal toxicity with acute renal insufficiency. Nephrotoxicity is usually caused by the deposition of **ABITREXATE** and 7-hydroxymethotrexate in the renal tubuli.

Skin and subcutaneous tissue disorders:

Less frequent: Erythema, pruritus, urticaria, photosensitivity, depigmentation, alopecia, ecchymosis, telangiectasia, acne, furunculosis. Psoriatric lesions may worsen by exposure to UV-radiation. Radiation dermatitis and sunburn may flare up by **ABITREXATE** administration.

A few cases of toxic epidermal necrolysis and Steven Johnson syndrome were reported.

Other disorders:

Less frequent: Other rare adverse effects related to or ascribed to the use of **ABITREXATE** are arthralgia/myalgia, diabetes, osteoporosis, lymphomas, opportunistic infections, vasculitis, and sudden death.

Incidental cases of anaphylactic reactions have been reported.

Also pancytopenia and sudden increase in the number of rheumatoid nodules have been reported in patients with rheumatoid arthritis.

Fatalities have occurred. Neurotoxic reactions are especially associated with the intrathecal use of **ABITREXATE**. Teratogenic effects and foetal deaths have been reported.

Precautions:

During the use of **ABITREXATE** the following laboratory tests are generally advised: hemograms, counting of the platelets and haematocrit; renal function tests and urine analysis; liver enzyme determination; chest X-ray is recommended. During the treatment of psoriasis and rheumatoid arthritis it is recommended to repeat those tests regularly: monthly haematology, every 1 – 3 months liver and kidney function.

Usually during antineoplastic treatment a more frequent control procedure is applied. On treatment initiation or a dose modification or during periods in which an enhanced risk on increased **ABITREXATE** blood levels (e.g. in case of dehydration) may develop, a more frequent monitoring is necessary.

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established. Transient deviation in liver function tests has often been observed after **ABITREXATE** administration and usually do not lead to therapy modification. Impairment in liver function just prior to administration and/or serum albumin level decrease may indicate serious liver toxicity and require further examination.

Lung function tests may be useful in case an **ABITREXATE** induced lung disease is suspected, in particular when initial base line values are available.

ABITREXATE induced lung disease is a potentially dangerous condition which may occur at any moment during therapy with dosages higher than 7,5 mg weekly. The condition is not always completely reversible. Pulmonary symptoms (in particular a dry, non-productive cough) may require treatment interruption and thorough examination. In the treatment of **ABITREXATE** induced (interstitial) pneumonitis after immediate discontinuation of therapy, corticosteroid treatment is indicated. In case of the occurrence of lung toxicity re-initiation of therapy is contra-indicated.

ABITREXATE should be used with extreme care in patients with infection, peptic ulcer, ulcerative colitis, debility and in the very young or aged.

Diarrhoea and ulcerative stomatitis require discontinuation of treatment because of the risk of

haemorrhagic enteritis and death by intestinal perforation.

In case of severe leucopenia occurring during treatment, bacterial infections could set in. When infection occurs, discontinuation of **ABITREXATE** and adequate antibacterial therapy is indicated.

In case of severe bone marrow depression blood or thrombocytes transfusion may be necessary.

Special care should be taken in the patients with decreased renal function as **ABITREXATE** elimination time is increased in renal dysfunction.

At the onset of nephrotoxicity also immediate discontinuation of therapy is indicated.

During **ABITREXATE** therapy and until at least three months after treatment with **ABITREXATE**, contraceptive precautions should be taken by female as well as male patients.

Thus far there are no indications for an increased risk of carcinogenicity in humans undergoing prolonged therapy, such as psoriasis patients. The data on the carcinogenicity risk in case of use of **ABITREXATE** by rheumatoid arthritis patients are limited.

While in general a low dose of **ABITREXATE** is applied in the treatment of psoriasis and rheumatoid arthritis, as compared to the doses used in antineoplastic therapy, intoxication and death may occur.

Patients should be fully informed on the risks of **ABITREXATE** therapy and should be instructed to report any manifestation of toxicity immediately.

It is recommended to carry out a liver biopsy in psoriasis and rheumatoid arthritis patients after a total cumulative dose of 1,5 g. Fibrosis of intermediate revering or any cirrhosis usually requires discontinuation of therapy. Although mild changes usually are no reason to avoid or discontinue therapy, **ABITREXATE** should be used with care in patients.

The combined administration of **ABITREXATE** and other potentially hepatotoxic drugs and alcohol should be avoided.

Lymphomas may develop in patients, treated with low dose **ABITREXATE.** Spontaneous remission may occur when **ABITREXATE** therapy is stopped; therefore, treatment with oncolytics is not necessarily indicated. First, it is necessary to stop **ABITREXATE** treatment, when this adverse event occurs. If remission fails to appear, an adequate treatment has to be started.

ABITREXATE should be used with great care in patients with hepatic or renal impairment. It should also be used cautiously in alcoholics or those with ulcerative disorders of the gastro-intestinal tract. With high-dose regimens, plasma concentrations of **ABITREXATE** and urinary excretion should be monitored. Precipitation of **ABITREXATE** or its metabolites in the renal tubules may be prevented by alkalinisation of the urine using sodium bicarbonate, maintaining an adequate urine flow, and the withholding of therapy until pleural or ascitic effusions, which may act as a depot for methotrexate, have been drained.

It is essential that examinations of blood and tests of renal and liver function should be made before, during and after each course of treatment with **ABITREXATE.** If there is a severe fall in the white cell or platelet counts, **ABITREXATE** should be withdrawn.

While preparing **ABITREXATE** injections protective gloves, a mask and safety goggles should be worn. The preparation of **ABITREXATE** has to take place in a vertical laminar air flow hood. Spillage of **ABITREXATE** should be washed with ample water.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See “Side-effects and Precautions”.

Folinic acid neutralises the immediate toxic effect of **ABITREXATE** on the bone marrow and is given by mouth, intramuscularly, by intravenous bolus injection, or by infusion as calcium folinate. When overdosage is suspected, the dose of calcium folinate should be at least as high as that of **ABITREXATE** and should be administered within the first hour; further doses are given as required. When average doses of **ABITREXATE** have an adverse effect, the equivalent of 12 mg of folinic acid may be given intramuscularly every 6 hours for 4 doses. The majority of a dose is excreted unchanged in the urine within 24 hours. Bound **ABITREXATE** may be retained in the body for many months.

Treatment is symptomatic and supportive.

IDENTIFICATION:

A, clear orange-brown solution.

PRESENTATION:

Abitrexate 50 Injection: Single 2 ml vial

Abitrexate 500 Injection: Single 20 ml vial

Abitrexate 1 g Injection: Single 10 ml vial

Abitrexate 5 g Injection: Single 50 ml vial

STORAGE INSTRUCTIONS:

Store below 25 ºC and protect from light.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS:

Abitrexate 50 Injection: T/26/63

Abitrexate 500 Injection: T/26/64

Abitrexate 1 g Injection: T/26/57

Abitrexate 5 g Injection: W/26/386

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Suite 1, Building 4, Ruimsig Office Park

Hole in One Road, Ruimsig

Roodepoort

DATE OF PUBLICATION OF THE PACKAGE INSERT:

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